

- (b) collecting data on the action potential, the one or more characteristics thereof, or one or more changes therein; and
C5 ~~(c) determining from said data the one or more ion channels that are affected by the test substance.~~

27. (Once Amended) The method of claim 26 in which the deconvolution of the action potential or its derivatives, the one or more characteristics thereof, or the one or more changes therein provides information on pathways or functional categories affected in the cell.

Please add the following new claim:

C60 --50. (New) The system of claim 1 which further comprises a second modified surface that separates the one or more electrically active cells and which comprises a repulsive layer.--

REMARKS

Claims 1-27 are pending in the present application. After entry of the amendment, claims 4, 13, 14, 16, 21, 22, 24, and 27 are amended to correct typographical errors, correct claim dependency, add clarity or for other reasons discussed in more detail below. Claim 50 is new and derives adequate support from page 16, lines 28-29 of the application, as filed. Additional support can be found in Fig. 9. (See, "Surface Mod 2" labeled layer "12.") Applicant respectfully submits that no new matter has been added. Reconsideration of the Examiner's rejections in view of these amendments and accompanying remarks is respectfully requested.

Counsel for applicant would like to thank the Examiner for the courtesy she extended in granting a personal interview, which was conducted on September 6, 2002. Dr. James Hickman, the applicant, and Dr. Earl Wagener, the Chief Executive Officer of the patent owner, Hesperos, Inc., would also like to express their gratitude for the opportunity to present the merits of the invention to the Examiner.

The Invention

As claimed, the invention is a system comprising a solid state microelectrode, a cell culture comprising one or more electrically active cells, an intervening layer, and software that comprises instructions, which can be executed by a computer. In particular, the intervening layer is recited in claim 1 as (i) comprising a surface modifying agent, and (ii) *positioned between the microelectrode and the one or more cells* of the cell culture such that a *high impedance seal is provided* at least in the vicinity of the one or more cells of the cell culture. Drawing the Examiner's attention to page 8, lines 11-15 of the application, as filed, the applicant has described a "high impedance" seal as one "that reduces the lateral flow of ions across the microelectrode from the surrounding medium, while permitting or facilitating the vertical flow of ions between the cell and the microelectrode. In this manner, the microelectrode is best suited to detect changes in the ion flux attributable to the cell and not due to the surrounding medium." Also, at page 9, lines 31-33 of the application, as filed, the applicant states that "such a device may further comprise an intervening layer that is acting as a high impedance seal and which is positioned between the microelectrode and the one or more cells of the cell culture, . . ." It goes without saying that any prior

reference alleged to anticipate the claimed invention or any combination of references alleged to render the claimed invention obvious must recite all the elements of the claimed invention, including an intervening layer.

The Section 102(b) Rejection

Claims 1-8, 12-14, and 23 stand rejected as allegedly being anticipated by Jung et al. Of the Jung et al. reference, the Examiner states at page 4 of the Office action that "Jung et al. discloses a biosensor system comprising a solid state electrode array where the microelectrodes are electroplated with platinum black and a silane SAM was formed on the array." As discussed during the recent interview, the Examiner is under the impression that Jung et al.'s disclosure includes an "intervening layer" because a silane self-assembling monolayer is described in the Jung et al. reference. This rejection is respectfully traversed.

A closer examination of Section III (A) of Jung et al. reveals, however, that the microelectrodes were electroplated with platinum black, which is a mixture of carbon and a reduced form of platinum metal obtained through the action of molecular hydrogen. Platinum black contains no surface Pt-O groups unlike platinum oxide (PtO_2), which is brown, or alkaline solutions of platinum, such as $[\text{Pt}(\text{OH})_6]^{2-}$. Over this "platinized" microelectrode array was "formed" a silane self-assembled monolayer of (aminoethylaminomethyl)phenethyltrimethoxysilane (PEDA). Formation of a SAM requires the presence of surface metal-oxygen groups, however, as discussed on page 245 of an *Introduction to Ultrathin Organic Films*, 1991, Academic Press, a copy of which is attached hereto as Appendix A. Essentially, the process described in Jung et

al. provides a SAM on the insulator surface, which has surface hydroxyl groups, but not on the microelectrode surface, which has been electroplated with platinum black and lacks the surface hydroxyl groups. Therefore, Jung et al. does not describe an intervening layer as required by claim 1 because, first, there is no SAM positioned between the microelectrode and the one or more cells of the cell culture. Second, because there is no SAM interposed between the microelectrode and the one or more cells, there can also be no intervening layer that acts as a high impedance seal, again as required by claim 1. Hence, the rejection based on Jung et al. cannot be reasonably sustained.

The rejection having been overcome, applicant respectfully requests that the rejection be withdrawn. Favorable reconsideration of the rejected claims is respectfully requested.

The Section 103(a) Rejection

Claims 1-14, 18-19, and 23-27 stand rejected as allegedly being rendered obvious over the proposed combination of Borkholder et al. and Jung et al. The Examiner remarks on page 6 of the Office Action that Borkholder et al. "doesn't clearly disclose a microelectrode as set forth in the claims, . . ." The Examiner further states on the same page that "[i]t would have been obvious to use the microelectrode of Jung et al. in the system and method of Borkholder et al. One would have been motivated to do so as a matter of substituting another suitable and known biosensor." This rejection is respectfully traversed.

Regardless of whether sufficient motivation in fact exists to combine the teachings of the two references, applicant respectfully asserts that the Examiner has failed to combine two references which, overall, remedy the deficiencies of Jung et al. Stated plainly, neither Jung et al. nor Borkholder et al. teach, suggest, or disclose an intervening layer as recited in independent claims 1 and 24. Accordingly, the Examiner has failed to carry her burden of making a *prima facie* showing of obviousness. This rejection cannot, therefore, be reasonably sustained and should be withdrawn. The rejection having been overcome, applicant respectfully requests favorable reconsideration of the rejected claims.

The Section 112, Second Paragraph, Rejections

Claims 1-27 stand rejected as being allegedly indefinite for failure to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of the claims addressed by the Examiner in her Office Action will be discussed in turn. In claim 1, the phrase "accompanying software" simply means that the system includes software that comprises instructions that can be implemented by a computer (i.e., computer-executable instructions). The software can certainly be stored on a computer-readable medium, such as a hard drive, magnetic tape, floppy disk, CD, or the like. Next dependent claims 4 and 14 have been amended to remove the antecedent basis problem and to cure the alleged improper Markush language. In claim 11, applicant asserts that a stem cell can be exposed to a differentiating factor at any time, and hence the claim is worded without a limitation as to "when" such exposure can or does take place. The phrase "similar molecules" has been deleted from claim 13.

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Claim 16 (applicant assumes that the Office Action includes a typographical error) has been amended to delete the first occurrence of "cadherins." The phrase "and the like" has been deleted from claim 21. Claim 22 has been amended to overcome the Examiner's rejection. The typographical error in claim 24 has been corrected. Claim 27 has been amended to make clear that the deconvolution involves an "action potential or its derivatives, the one or more characteristics thereof, or the one or more changes therein." Also applicant respectfully asserts that the metes and bounds of the phrase "functional category" would be apparent to one of ordinary skill in the art, particularly in view of the applicant's discussion, which is found, for example, in Section 6.4 of the application, as filed. See, for instance, Table 1 and Section 6.4.1. wherein 14 genetic categories are referenced in Riley et al. and six broad categories are discussed in Section 6.4.1. et seq.

Applicant is Entitled to the Benefit of the Filing Date of the Provisional Patent Application

The Examiner correctly notes in the Office Action that the earlier-filed provisional application is a compilation of two grant proposals. The Examiner is incorrect, however when she states that the provisional application "does not disclose or contemplate the generic invention as presently recited in the claims." Indeed the elements of claim 1, as described above under the Section "The Invention," can be readily appreciated by a fair reading of the provisional application.

First, in the Abstract (page 1, referring to page numbers at upper right-hand corner), the proposal describes the marriage of solid state electronics with a reporter

element of electronically active cells (lines 1-4), the use of algorithms to analyze action potential peak shape differences (lines 18-19) and the use of surface chemistry to create a gigohm seal to recreate the interface that enables patch-clamp electrophysiology (i.e., an intervening layer that acts as a high impedance seal). At page 3, beginning of the third paragraph, this "patch-clamp like seal" is described as being "between the cell and the microelectrode." At page 5, third paragraph, surface modification is again associated with a "high impedance seal." The "establishment of high impedance seals on the microelectrode substrates" is again mentioned at page 15, middle of the first paragraph. The notion of deconvolution is described on page 16, first full paragraph, wherein the applicant states that "[s]ignals corresponding to changes in the membrane potential will be deconvoluted using the methods outlined in Figure 6." Section 2.2.2, at page 20, describes the creation of the microelectrode-neuron interface, including the creation of a high impedance seal.

Second, and redundantly, under "Specific Aims" on page 39, an array of electrically active cells (line 6) are described as being part of a real time assay (line 10), which includes algorithms (line 17) for deciphering changes in action potentials (line 15) and a patch-clamp like seal between the cell and the microelectrode (lines 22-23). The approach is described as being applicable to "any cell type where we can monitor electrical changes in the membrane potential." See, page 40, bottom of fourth full paragraph. References to generation of algorithms and establishment of high impedance seals abound elsewhere in the document.

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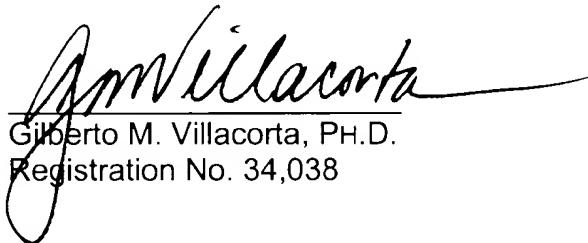
Accordingly, applicant respectfully concludes that at least the breadth of the invention, as presently claimed, finds adequate written support in the provisional patent application. The Examiner's reconsideration of this issue and her agreement with the applicant's conclusion are cordially solicited.

CONCLUSION

Applicant believes that the pending claims recite subject matter that is novel and non-obvious over the disclosure of the prior art of record and which satisfies all the statutory requirements of patentability. Favorable consideration of such subject matter is respectfully requested.

No fees are believed to be necessary. However, the Commissioner is authorized to charge any shortage in fees due in connection with the filing of this Amendment, or credit any overpayment, to Deposit Account No. 50-1710.

Respectfully submitted,



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APPENDIX

MARKED-UP VERSION OF CLAIMS SHOWING CHANGES MADE

4. (Once Amended) The system of claim 1 in which the instructions comprise data processing instructions [are further] capable of receiving input data comprising data on ion flux through ion channels selected from the group consisting of sodium channels, potassium channels, calcium channels, [or] and combinations thereof.

13. (Once Amended) The system of claim 12 in which the self-assembling monolayer comprises a silane, a thiol, isocyanide, polyelectrolyte [or similar molecules] or combinations thereof.

14. (Once Amended) The system of claim 1 in which the instructions comprises data processing instructions [is further] capable of receiving input data comprising data on the changes in the temporal description of the action potential.

16. (Once Amended) The system of claim 15 in which the cell anchorage molecules comprise antibodies, antigens, receptor ligands, receptors, lectins, carbohydrates, enzymes, enzyme inhibitors, biotin, avidin, streptavidin, [cadherins,] RGD-type peptides, integrins, cadherins, modified lipids, or combinations thereof.

21. (Once Amended) The system of claim 20 in which the polymer comprises cellulose, methylcellulose, or dextran [and the like].

22. (Once Amended) The system of claim 1 in which the intervening layer [can be characterized as either] comprises an attractive layer [or a repulsive layer].

24. (Once Amended) A method of determining one or more ion channels that are affected by a test substance comprising:

- (a) contacting a substance to be tested with a device comprising a solid state microelectrode; a cell culture including one or[e] more cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics; and an intervening layer that is acting as a high impedance seal and which is positioned between said microelectrode and said cell culture;
- (b) collecting data on the action potential, the one or more characteristics thereof, or one or more changes therein; and
- (c) determining from said data the one or more ion channels that are affected by the test substance.

27. (Once Amended) The method of claim [24] 26 in which the deconvolution [leads to] of the action potential or its derivatives, the one or more characteristics thereof, or the one or more changes therein provides information on pathways or functional categories affected in the cell.

Please add the following new claim:

--50. (New) The system of claim 1 which further comprises a second modified surface that separates the one or more electrically active cells and which comprises a repulsive layer.--